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AMG334

Clinical Trial Protocol CAMG334A2401 / NCT03927144

A 12-month prospective, randomized, interventional, global, multi-center, active-controlled study comparing sustained benefit of two treatment paradigms (erenumab qm vs. oral prophylactics) in adult episodic migraine patients

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List of abbreviations

γ-GT	Gamma-glutamyl transferase
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
b.i.d.	twice a day
BMI	Body Mass Index
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CD-ROM	compact disc – read only memory
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CK	creatinine kinase
CO_2	carbon dioxide
COAR	Clinical Operations, Analytics & Regions
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
HIV	human immunodeficiency virus
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology

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LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLQ	lower limit of quantification
MABEL	minimum anticipated biological effect level
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
ml	milliliter(s)
MRSD	maximum recommended starting dose
NCDS	Novartis Clinical Data Standards
NOVDD	Novartis Data Dictionary
o.d.	once a day
p.o.	oral
PA	posteroanterior
PD	pharmacodynamic(s)
PIP	pediatric investigation plan
PK	pharmacokinetic(s)
PTA	Post-trial access
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
s.c.	subcutaneous
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoC	Standard of Care
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all

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	study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 02

Amendment rationale

The purpose of this amendment is to provide Post-Trial Access (PTA) to erenumab for eligible patients completing visits through week 52 of the Core Phase. Patient eligibility will be determined by the investigators opinion as follows: 1) patients treated with erenumab must have benefited from erenumab treatment and 2) patients on Standard of Care (SoC) oral prophylactic must be in need of a treatment switch. PTA to erenumab will be provided for up to 52 weeks (based on continued benefit of erenumab treatment) in all eligible patients.

The PTA-Open-Label Treatment Period (Extension Phase) will evaluate further long-term safety and clinical benefit of erenumab. [redacted]

During the Extension Phase patients will be administered study drug at the study site at quarterly study visits. Between the quarterly visits patients will have study drug injections every 28 days either 1) administered by the site staff at brief injection visits at site or 2) self-administered at home with documented on-site training for correct injection procedure.

In addition, details for potential trial conduct changes due to the COVID-19 pandemic have been incorporated in this protocol amendment. Updates have been made to the relevant protocol sections.

Changes to the protocol

- Protocol Summary
  - Updated to add details for revised study design, removed Follow-up visit, clarified Exclusion criteria language for prohibited medications [redacted]
- Section 3.0 Study design
  - Added Core Phase text, removed Follow-Up visit, provided details for PTA-Extension Phase with updated Figure 3-1 and added details for CSR requirements.
- Section 4.1 Rationale for study design
  - Added rationale for PTA-Open-Label Treatment Period
- Section 4.3 Rationale for choice of control drugs (comparator)
  - Deleted table describing SoC oral prophylactic migraine drugs available.
- Section 4.5 Risks and benefits
  - Added Investigators Brochure as a reference for risks and benefits
- Section 5.2 Exclusion criteria
  - Revised Exclusion Criteria 5 and 8 for clarity, removed text with reference to during treatment period throughout section as this is not an exclusion criteria and updated Exclusion Criteria 18 for clarity.
- Section 6.1 Study treatment

[redacted]

  - Revised Core Phase and added Extension Phase drug details in Table 6-1, and added details for Extension Phase and Section 6.1.3 and Section 6.1.4 updated for clarity.
- Section 6.2.2 Prohibited medication and Section 6.2.3 Rescue medication
  - Updated prohibited medication section for clarity and added details for rescue medication collection in eCRF pages.
- Section 6.3.2 Treatment assignment, randomization
  - Updated details for Core Phase randomization and added Extension Phase details.
- Section 6.6.1 Treatment Compliance
  - Added details for Core and Extension Phase
- Section 6.7 Preparation and dispensation
  - Added guidance section for COVID-19 related to delivery of study drug and self-administration of study drug for patients affected by the pandemic.
- Section 6.7.1.1 Handling of study treatment
  - Added details for self-administration of study drug.
- Section 6.7.2 Instruction for prescribing and taking study treatment
  - Added details for self-administration of study drug and provided clarity for dosing windows.
- Section 7 Informed consent procedures
  - Updated to add guidance for COVID-19 for signing of general informed consent documents and added details for patients that had self-administration of study drug and the requirements to sign an ICF to document the process.
- Section 8 Visit schedule and assessments
  - Added details for Extension Phase in text, updated Core Phase text and assessment Table 8-2 for Extension Phase assessments. Revised guidelines for dosing windows for clarity and included a guidance section for COVID-19 related to alternatives for conducting study visits with options to use phone calls, virtual visits etc. for patients affected by the pandemic.
- Section 8-3 Efficacy
  - Added guidance for COVID-19 that PRO scales may still be collected by using the eDiary for patients impacted due to the pandemic [redacted]
- Section 8.4 Safety
  - Included guidance for COVID-19 indicating that regular phone or virtual calls would occur to monitor the safety of patients impacted due to the pandemic and updated schedule for physical exam.
- Section 8.4.1 Laboratory evaluations
  - Introduced guidance for COVID-19 to indicate that collection of laboratory samples may need to be modified for patients impacted due to the pandemic.
- Section 8.4.3 Pregnancy

[redacted]

- Introduced guidance for COVID-19 to indicate that urine pregnancy tests may be used at home instead of conducted in the clinic when serum or urine pregnancy tests were scheduled for patients impacted due to the pandemic.

[redacted]

- Section 9.1
  - Introduced additional reasons for discontinuation of study treatment during the Extension Phase and added a section to provide clarity for what occurs during the Core Phase when a patient discontinues the study.
- Section 9.2 Study completion and post-study treatment
  - Provided details for Extension Phase
- Section 12 Data analysis and statistical methods
  - Provided details that Core and Extension phase data would be analyzed separately.
- Section 12.1 Analysis sets
  - Introduced an analysis set for the Extension Phase.
- Section 12.5.2 Safety endpoints
  - Provided details that safety data collected during Extension Phase would be analyzed separately and deleted summary of AEs of special interest since analysis is not conducted.

[redacted]

- Section 13.3 Publication of study protocol and results
  - Introduced details for clinical study reports.
- Section 16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements
  - Provided guidance in footnote to Table 16-2 for collection of INR if patients have a liver event.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

[redacted]

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 01

Amendment Rationale

The purpose of this global amendment is to update the protocol language to reflect feedback received from Health Authorities on contraception/pregnancy language and on standard of care practices globally from participating investigators. Additionally, text was added to clarify protocol text language, typographical errors, and grammatical errors.

Changes to the protocol

- Protocol Summary
  - The Protocol Summary was updated to reflect the updates made in the protocol below.

[redacted]

- Section 3 Study design
  - Clarified discrepancy on study completion and the Follow-up Visit that it should occur 16 weeks after the Week 52 visit
- Section 5.1 Inclusion Criteria
  - Inclusion criterion 6 updated to align with exclusion criterion 4
- Section 5.2 Exclusion Criteria
  - Exclusion criterion 4 was updated to reflect guidance documents and investigator practice for prior treatment failures.
  - Exclusion criterion 20 has been updated to include language related to highly effective methods of contraception.
- Section 6.1.1 Investigational and Control Drugs
  - Capsule was added as a possible formulation for oral prophylactics.
- Section 6.1.3 Treatment arms/groups
  - The stratification cap was re-iterated to provide better clarity.
- Section 6.2.2 Prohibited Medication
  - Text table was updated to align with exclusion criterion 22
- Section 6.5 Dose escalation and dose modification
  - Added statement clarifying source documentation of dose changes
  - Section 6.6.1 Treatment compliance

[redacted]

  - Clarified that documentation to be captured only in the source documents and drug accountability log for standard of care
- Table 8-1 Assessment Schedule
  - Updated table to reflect amended protocol text
- Section 8.3.1 Migraine days
  - Added text on additional data points captured in the eDiary related to vertigo and menses
- Table 8-3 Safety Assessments
  - Clarified that height and weight will only be captured at full physical exams
- [redacted]
- Section 10.1.1 Adverse Events
  - Clarified that adverse event collection should only begin at Treatment/Day 1 visit
- Section 12.4 Analysis of the primary endpoint(s)
  - Clarified that the analysis is comparing to oral prophylactics
- Section 12.5 Analysis for the secondary endpoints
  - Updated language to reflect updates to objectives and endpoints
- Section 12.8 Sample size calculation
  - Clarified that the analysis is comparing to oral prophylactics

[redacted]

Protocol summary

Table 1-1 Protocol Summary

Protocol number	AMG334A2401
Full Title	A 12-month prospective, randomized, interventional, global, multi-center, active-controlled study comparing sustained benefit of two treatment paradigms (erenumab qm vs. oral prophylactics) in adult episodic migraine patients
Brief title	Study of sustained benefit of erenumab in adult episodic migraine patients
Sponsor and Clinical Phase	Novartis & Amgen Phase IV
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to compare the sustained long-term benefit between two treatment paradigms of migraine prophylactic agents (erenumab versus a control arm of oral prophylactics) in episodic migraine patients who have previously failed 1 to 2 prophylactic migraine treatments. Data from this study, in addition to the data generated thus far in the clinical program, will provide important data for clinicians treating migraine patients, particularly for patients who have previously failed existing preventative treatments, as there are limited treatment options. Subsequently it will determine if early use of erenumab during a treatment algorithm is associated with a favorable long-term sustained benefit. The PTA-Open-Label Treatment Period will provide additional information for longer term safety and will provide an assessment of effectiveness.
Primary Objective(s)	The primary objective is to demonstrate the superiority of subcutaneous erenumab compared to oral prophylactic(s) on sustained benefit defined as % subjects completing one-year on the randomized treatment and achieving at least a 50% reduction from baseline in monthly migraine days at month 12.
Secondary Objectives	Objective 1: To evaluate the effect of erenumab compared to oral prophylactic(s) on overall subject retention defined as % subjects completing treatment period at Month 12 on initially assigned treatment Objective 2: To evaluate the effect of erenumab compared to oral prophylactic(s) on the change from baseline in monthly migraine days during the treatment period Objective 3: To evaluate the effect of erenumab compared to oral prophylactic(s) on the subject's assessment of the change in clinical status since the start of treatment as measured by the Patients' Global Impression of Change (PGIC) Scale
Study design	This study uses a single-cohort, 2-treatment arm (erenumab versus SoC oral prophylactic treatment), parallel-group randomized (2:1 [erenumab (70 mg or 140 mg): SoC oral prophylactic]), open-label design in adult patients with episodic migraine who have previously failed 1 or 2 prophylactic migraine treatments. The following periods are included in the study design, with study visits at 4-week intervals after completion of screening: • **Screening Period (0-2 weeks) –** Required for all subjects to assess initial eligibility and to obtain informed consent

[redacted]

	• **Baseline Period (4 weeks) –** All subjects successfully completing the Screening Period will be invited to participate. Eligibility for randomization will be assessed based on migraine frequency and diary compliance during this period. Randomization will be stratified by prior prophylactic migraine medication treatment failure (due to insufficient efficacy or poor tolerability) reported during Screening/Baseline Period: 1 treatment failure (TF1) vs 2 treatment failures (TF2). A cap of 30% randomized subjects to the TF2 strata will be implemented. The stratification and 30% cap will be implemented within IRT. • **Open-Label Randomized Treatment Period (52 weeks) –** All subjects successfully completing the Baseline Period will be invited to participate. Eligible subjects will be randomized 2:1 to one of two treatment arms [erenumab s.c. q.m. versus SoC oral prophylactic (active comparator)]. Only monotherapy will be allowed in both arms and no concomitant use of other prophylactics for migraine specifically should be used. At the end of this period, the final assessment to address the effect of erenumab compared to SoC oral prophylactic cycling on the net benefit and related objectives will occur. The last dose for erenumab will occur at Week 48 (monthly dose) and the last dose for SoC will occur at Week 52. • Switching: Treatment (failure) status and decision on whether or not to switch to a new treatment will be checked at every visit and will be based on investigator and subject discretion (based on efficacy/tolerability/satisfaction but not based on pre-specified cutoffs for certain parameters). In both arms, switching will be allowed within approved prophylactics in the respective country for prophylaxis of migraine. • **PTA-Open-Label Treatment Period (52 Weeks) –** Patients completing visits through week 52 of the Core Phase will be eligible to participate. Patient eligibility will be determined by the investigators opinion as follows: 1) patients treated with erenumab must have benefited from erenumab treatment and 2) patients on Standard of Care (SoC) oral prophylactic must be in need of a treatment switch. PTA to erenumab will be provided for up to 52 weeks (based on continued benefit of erenumab treatment) in all eligible patients; this will ensure erenumab access until country-level launch and subsequent reimbursement decision in all countries. Should a treatment gap exist between the Core and Extension Phase due to a delay of HA/EC approvals or other administrative/logistical reasons, the subject may enter the PTA-Open-Label Treatment Period at a later time. During this treatment gap the patient would remain in the main study and is allowed to be treated with any medication as deemed appropriate by the investigator to manage the patient's migraines. Upon HA and EC approval of the PTA-Open-Label Treatment Period, the patient will then be administered study drug corresponding to the Week 52 dose and will continue dosing every 4 weeks as per protocol. Patients will be required to follow all protocol requirements for treatments allowed and for prohibited medications (Section 6.2.2). End of Trial will occur when the last subject completes their last visit (LPLV) of the study. A final study report will be prepared and finalized for all data after all subjects have completed their respective last visit (LPLV).
Population	The study population will consist of adult male and female subjects with a documented history of episodic migraine (4 to 14 baseline migraine days), who have failed 1 or 2 previous migraine prophylactic treatments for lack of efficacy or

[redacted]

	tolerability. The goal is to randomize approximately 600 subjects in approximately 100 centers worldwide.
Key Inclusion criteria	• Adults ≥18 of age upon entry into screening. • Documented history of migraine (with or without aura) ≥12 months prior to screening. • ≥4 and <15 days per month of migraine symptoms (based on ICHD-3 criteria) on average across 3 months prior to screening based on retrospective reporting. • <15 days per month of headache symptoms (i.e., migraine and non-migraine) • Subjects in need for switching by documented failure of 1 or 2 prophylactic therapies in the last 6 months due to either lack of efficacy or poor tolerability (see list of prophylactic therapies in Exclusion Criteria 6 and definition for lack of efficacy and poor tolerability). For subjects with 1 prior treatment failure, the failure should have occurred in the last 6 months. For subjects with 2 prior treatment failures, the second treatment failure should have occurred in the last 6 months. • During baseline period, confirmed migraine frequency of 4 to 14 migraine days and <15 days of headache symptoms. • During baseline period, ≥80% compliance with the headache diary.
Key Exclusion criteria	• Older than 50 years of age at migraine onset. • Lack of efficacy or poor tolerability with > 2 treatments from the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are: Category 1: Divalproex sodium, sodium valproate Category 2: Topiramate Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol) Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline) Category 5: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran) Category 6: Flunarizine, verapamil Category 7: Lisinopril, candesartan Efficacy failure is defined as no meaningful reduction in headache frequency, duration, and/or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment. Tolerability failure is defined as documented discontinuation due to adverse events of the respective medication during the last 6 months prior to screening The following scenarios do not constitute lack of therapeutic response: • Lack of sustained response to a medication • Patient decision to halt treatment due to improvement • Used a prohibited medication from the 7 categories of prior prophylactic medications within 3 months prior to the start of and during baseline for a non-migraine indication if dose is not stable. • Device, or procedure that potentially may interfere with the intensity or number of migraine days within 2 months prior to the start of or during baseline.

[redacted]

	• Exposure to botulinum toxin in the head and/or neck region within 4 months prior to the start of the baseline period, during the baseline period
	• Taken the following for any indication in any month during the 2 months prior to the start of the baseline period:
	  • Ergotamines or triptans on ≥ 10 days per month, or
	  • Simple analgesics (non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) on ≥ 15 days per month, or
	  • Opioid- or butalbital-containing analgesics on ≥4 days per month.
	• Previous exposure to erenumab or exposure to any other prophylactic CGRP-targeted therapy.

Study treatment	• Erenumab (70 mg or 140 mg) in 70 mg/1mL pre-filled syringes • Locally approved oral prophylactics
Efficacy assessments	• Migraine days • Patient study completion
Key safety assessments	• Adverse events • Physical examinations • Laboratory evaluations • ECG
Other assessments	**Patient Reported Outcomes (PROs)** [redacted] • Patients' Global Impression of Change (PGIC) [redacted]

Data analysis	The primary analyses will compare the proportion of subjects who achieve a net benefit between erenumab vs oral prophylactics. A Cochran-Mantel-Haenszel (CMH) test stratified by number of previous treatment failures (1 vs. 2) will be used under a 2-sided significance level of 0.05 to evaluate the association between the net benefit rate and the treatment.
	The secondary analysis will be handled as such:
	• Proportion of subjects completing the study at month-12 on the randomized treatment
	  • This variable will be analyze same as that of the primary analysis.
	• Global satisfaction as measured by PGIC at month 12 as per randomized treatment
	  • Patient will be considered as responder if PGI-I score is 5, 6, or 7. Proportion of responders based on PGI-I score at month 12 will be analyzed same as that of the primary endpoint.
	• Cumulative average change from baseline on the monthly migraine days during the treatment period (month 1-12)
	  • The average of monthly migraine days will be obtained cumulatively at each month across 12 months. The cumulative average change from

[redacted]

	baseline on the monthly migraine days will be derived using difference between cumulative average at each month and baseline monthly migraine days. The change from baseline will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit.
Key words	Erenumab, AMG334, migraine, episodic, headache, CGRP

1 Introduction

1.1 Background

Migraine is one of the most common neurological disorders with a high global prevalence, significant socio-economic burden and substantial impairment and disability of affected patients (2017). It is mainly characterized by recurrent headache lasting 4-72 hours and is usually accompanied by other neurological disturbances, nausea, and vomiting. The patient burden and disability as well as the societal impact increase with higher attack frequency, which is why the spectrum of migraine disorders is typically described according to frequency of migraine days per month. "Episodic migraine" (EM) is characterized by the presence of up to 14 migraine days per months, while "Chronic migraine" (CM) is defined as 15 or more headache days per months, at least 8 out of which have to be typical migraine days.

Migraine patients are currently being treated prophylactically by a variety of drug classes, many of them being used off-label and often based on insufficient or limited evidence. Common prophylactic drugs or drug classes used include beta-blockers, anti-epileptic agents (including topiramate and valproate), antidepressants (mainly amitriptyline and venlafaxine), certain calcium channel blockers (such as flunarizine and verapamil), and certain angiotensin-converting-enzyme inhibitor/angiotensin II receptor blockers (ACE/ARBs such as lisinopril and candesartan). Botulinum toxin (Botox®) is approved in US and the majority of the EU countries for CM use, but not for EM.

All of these therapies are commonly associated with either insufficient efficacy and/or substantial tolerability issues that often leads to treatment discontinuation in migraine patients. For example, in a recent claims database analysis in chronic migraine, persistence of oral prophylactics at one year, irrespective of class, was as low as 13-16% (Hepp et al 2016), therefore reflecting a high unmet medical need for new therapies. The standard of care also varies significantly across different geographies and treatment decisions are often made on a case-by-case basis without consensus on treatment guidelines.

Based on emerging evidence, calcitonin gene-related peptide (CGRP) is a neuropeptide that prominently contributes to migraine pathophysiology. The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-neurovascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal nucleus (Wang et al 1995, Zimmermann et al 1996, Durham 2006). The CGRP pathway was an attractive target for the development of a migraine-specific prophylactic therapy with the aim of minimizing migraine days and improving patient quality of life in this common and often disabling disorder.

[redacted]

Erenumab (AMG334) is a monoclonal antibody targeting the CGRP receptor, that is administered once monthly via subcutaneous injection. Erenumab was approved by the FDA on 17 May 2018 and EMA on 26 July 2018 for migraine prevention with an approved monthly dose of 70 mg or 140 mg. The benefits and safety of Aimovig were studied in four clinical trials involving >2600 patients and has been shown to be an effective and well-tolerated treatment for both episodic (Goadsby et al 2017, Study 20120296) and chronic migraine (Tepper et al 2017, Study 20120295). Results were consistently robust across different studies and different subgroups of patients, including patient groups with high unmet need such as those who have failed one or more prior prophylactic therapies due to lack of efficacy or poor tolerability.

The initial phase 2 dose finding study in episodic migraine (Sun et al 2016, Study 20120178) included an ongoing 5-year open-label extension phase. In a pre-specified interim analysis after all ongoing patients have completed one year of treatment, sustained efficacy has been shown with a long-lasting reduction from baseline of approximately 5 monthly migraine days and with 65% of patients achieving a 50% responder rate in the last month (Ashina et al 2017). Other recently available longer-term data after one year from studies 20120295 and 20120296 have also confirmed that the retention remains high (75-80% range at one year) and that the efficacy with continued erenumab treatment is sustained over time.

No active comparator studies were conducted in the pivotal program. With all existing standard of care treatments, no clearly defined, evidence-based and commonly accepted treatment algorithms exist. Choice of a treatment is heterogeneous across geographies and highly dependent on both individual experience of the treating physician as well as particular patient profiles. Due to the low persistence of oral prophylactics, switches between therapies are common and usually lead to inadequate longer-term disease control, particularly as many therapies require titration.

Given the emerging erenumab clinical profile including the available data in treatment failure patients, one key question is if early use of erenumab during a treatment algorithm is associated with a favorable long-term sustained benefit and how erenumab compares with oral prophylactics over one year in a real world setting.

1.2 Purpose

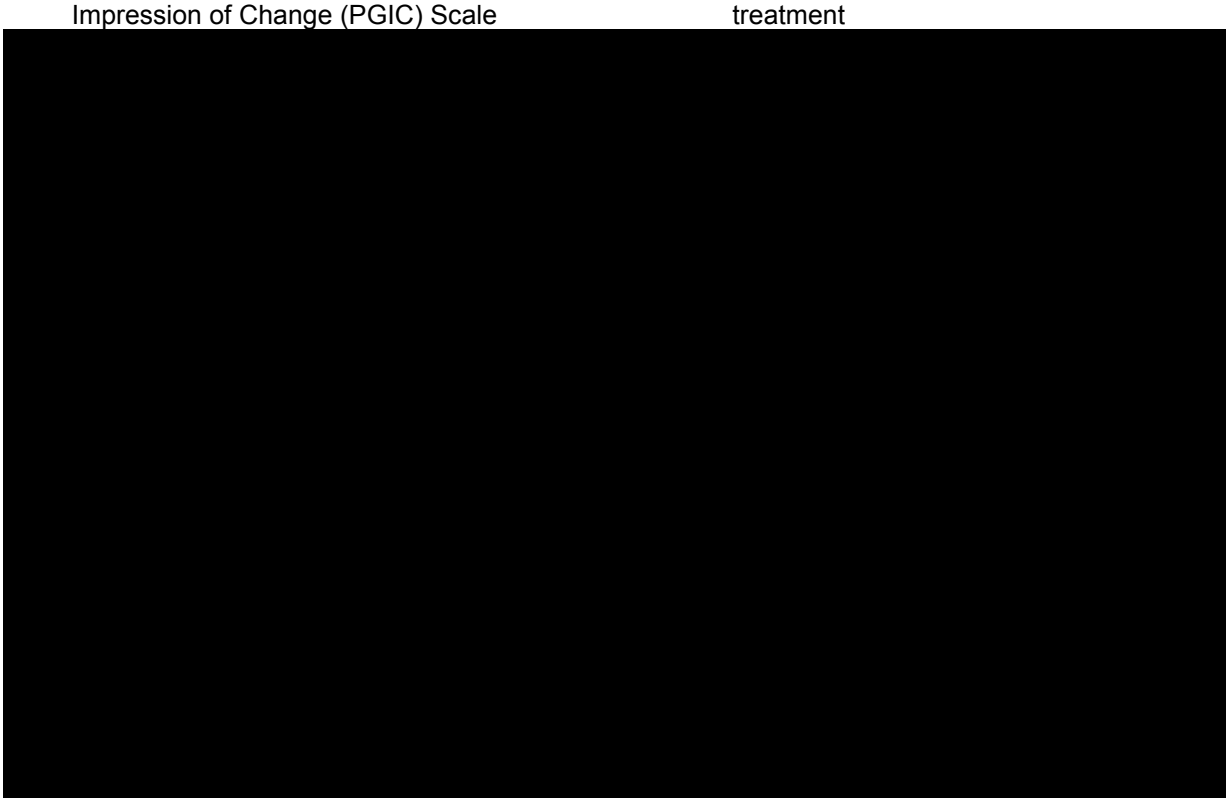
The purpose of this study is to compare the sustained long-term benefit between two treatment paradigms of migraine prophylactic agents (erenumab versus a control arm of oral prophylactics) in episodic migraine patients who have previously failed 1 to 2 prophylactic migraine treatments. Data from this study, in addition to the data generated thus far in the clinical program, will provide important data for clinicians treating migraine patients, particularly for patients who have previously failed existing preventative treatments, as there are limited treatment options. Subsequently it will determine if early use of erenumab during a treatment algorithm is associated with a favorable long-term sustained benefit.

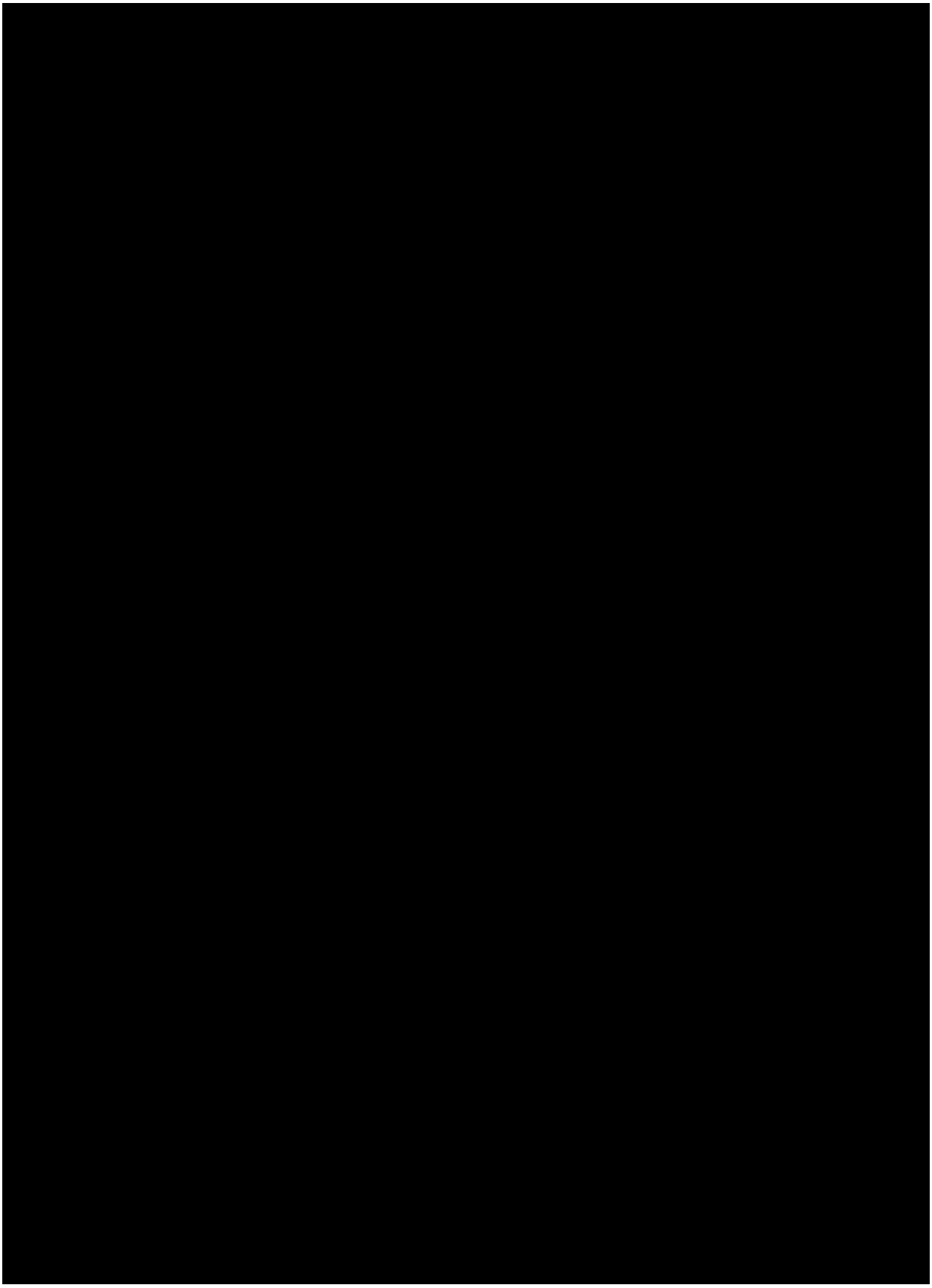
[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the superiority of subcutaneous erenumab compared to oral prophylactics on sustained benefit defined as % subjects completing one-year on the randomized treatment and achieving at least a 50% reduction from baseline in monthly migraine days at month 12.	• Proportion of subjects who complete initially assigned treatment and achieve at least 50% reduction from baseline in monthly migraine days at Month 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of erenumab compared to oral prophylactics on overall subject retention defined as % subjects completing treatment period at Month 12 on initially assigned treatment	• Proportion of subjects completing the treatment period at Month 12 on the initially assigned treatment
• To evaluate the effect of erenumab compared to oral prophylactics on the change from baseline in monthly migraine days during the treatment period	• Cumulative average change from baseline on the monthly migraine days during the treatment period for subjects on the initially assigned treatment (Months 1-12)
• To evaluate the effect of erenumab compared to oral prophylactics on the subject's assessment of the change in clinical status since the start of treatment as measured by the Patients' Global Impression of Change (PGIC) Scale	• Proportion of responders (PGI-I score ≥5) as measured by PGIC at month 12 for subjects completing the treatment period at Month 12 on initially assigned treatment





[redacted]

3 Study design

This study uses a single-cohort, 2-treatment arm (erenumab versus SoC oral prophylactic treatment), parallel-group randomized (2:1 [erenumab (70 mg or 140 mg): SoC oral prophylactic]), open-label design in adult patients with episodic migraine who have previously failed 1 or 2 prophylactic migraine treatments. The following periods are included in the study design, with study visits at 4-week intervals after completion of screening:

Core Phase:

- **Screening Period (0-2 weeks) –** Required for all subjects to assess initial eligibility and to obtain informed consent
- **Baseline Period (4 weeks) –** All subjects successfully completing the Screening Period will be invited to participate. Eligibility for randomization will be assessed based on migraine frequency and diary compliance during this period. Randomization will be stratified by prior prophylactic migraine medication treatment failure (due to insufficient efficacy or poor tolerability) reported during Screening/Baseline Period: 1 treatment failure (TF1) vs 2 treatment failures (TF2). A 30% cap of randomized subjects to the TF2 strata will be implemented. The stratification and 30% cap will be implemented within IRT.
- **Open-Label Randomized Treatment Period (52 weeks) –** All subjects successfully completing the Baseline Period will be invited to participate. Eligible subjects will be randomized 2:1 to one of two treatment arms [erenumab s.c. q.m. versus SoC oral prophylactic (active comparator)]. Only monotherapy will be allowed in both arms and no concomitant use of other prophylactics for migraine specifically should be used. At the end of this period, the final assessment to address the effect of erenumab compared to SoC oral prophylactic cycling on the net benefit and related objectives will occur. The last dose for erenumab will occur at Week 48 (monthly dose) and the last dose for SoC will occur at Week 52.
    - Switching: Treatment (failure) status and decision on whether or not to switch to a new treatment will be checked at every visit and will be based on investigator and

[redacted]

subject discretion (based on efficacy/tolerability/satisfaction but not based on pre-specified cutoffs for certain parameters). In both arms, switching will be allowed within approved prophylactics in the respective country for prophylaxis of migraine.

Extension Phase

- **Post-Trial Access Open-Label Treatment Period (52 weeks)** - Patients completing visits through week 52 of the Core Phase will be eligible to participate. Patient eligibility will be determined by the investigators opinion as follows: 1) patients treated with erenumab must have benefited from erenumab treatment and 2) patients on Standard of Care (SoC) oral prophylactic must be in need of a treatment switch. PTA to erenumab will be provided for up to 52 weeks (based on continued benefit of erenumab treatment) in all eligible patients; this will ensure erenumab access until country-level launch and subsequent reimbursement decision in all countries.
  Should a treatment gap exist between the Core and Extension Phase due to a delay of HA/EC approvals or other administrative/logistical reasons, the subject may enter the Extension Phase at a later time. During this treatment gap, the patient would remain in the main study and is allowed to be treated with any medication as deemed appropriate by the investigator to manage the patient's migraines. Upon HA and EC approval of the Extension Phase, the patient will then be administered study drug corresponding to the Week 52 dose and will continue dosing every 4 weeks as per protocol. Patients will be required to follow all protocol requirements for treatments allowed and for prohibited medications (Section 6.2.2).

End of Trial will occur when the last subject completes their last visit (LPLV) of the study.

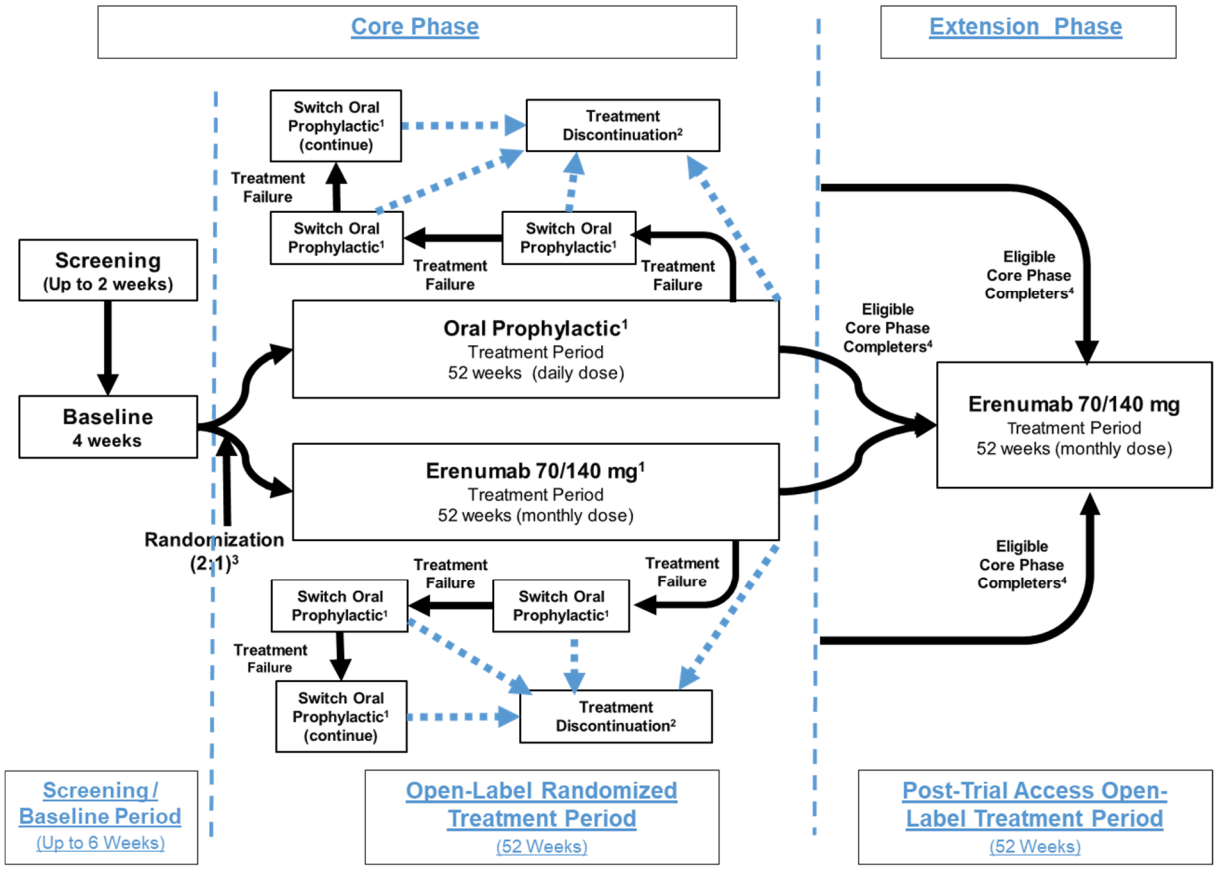
Note: Treatment discontinuation does not imply study discontinuation. Every effort should be attempted to ensure subjects complete the study visits event if treatment is discontinued. After study completion, post-trial access to erenumab will be offered to the study participants as needed.

The primary analysis will occur when the last patient completes the Core Phase, prior to the end of the Extension Phase. The main study report will be prepared and finalized at this time for all data from the Core Phase.

An additional study report will be prepared for the Extension Phase after all patients have completed their respective last visit (LPLV) of the Extension Phase and will report data for the Extension Phase.

[redacted]

Figure 3-1 Study Design Schematic



[1] Dose adjustments may be done if allowed per label and is not a treatment failure. Switching to oral prophylactic in the erenumab arm or switching to a different oral prophylactic in oral prophylactic arm is allowed

[2] Treatment Discontinuation does not imply study discontinuation. Every effort should be attempted to ensure subjects complete the study visits even if treatment is discontinued.

[3] Stratification based on Prior prophylactic migraine treatment - 1 prior treatment failure (70%) vs 2 prior treatment failures (30% cap)

[4] "Eligible Core Phase Completers" are patients that complete visits through Week 52 on or off of study drug and are either benefitting from erenumab treatment or are in need of a treatment switch.

[redacted]

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall (parallel, cross-over, sequential, factorial)	This will be a parallel study design. During the development program placebo-controlled studies only were conducted. This study will provide data on erenumab's efficacy and safety when compared head-to-head to SoC oral prophylactics.
Randomization (strata, allocation ratio)	Eligible subjects will be randomized 2:1 to one of two treatment arms (erenumab versus SoC oral prophylactic(s)) and will be stratified by prior prophylactic migraine medication treatment failure (due to efficacy or tolerability): 1 treatment failure (TF1) vs 2 treatment failures (TF2) with a cap of 30% to the TF2 strata. Unequal randomization favoring the erenumab treatment arm is expected to facilitate recruitment, generate additional data on TF1 to complement previous studies on TF2, and to determine if early use of erenumab during the treatment algorithm is associated with a favorable long-term sustained benefit. This randomization will allow for additional long-term efficacy and safety data on erenumab
Open-label during core phase	Given the difference in treatments (injectable vs. varied oral treatments), adequate blinding will not be possible.
PTA-Open-Label Treatment Period	The PTA-Open-Label Treatment Period is a mechanism to provide 52 weeks of PTA of erenumab for patients who completed visits through Week 52 of the Core Phase (see Section 3.0 for details)

4.2 Rationale for dose/regimen and duration of treatment

In order to capture real world, dose/regimen will follow the approved label. After regulatory review, erenumab was approved by FDA and EMA as a monthly treatment. The recommended dose is 70 mg of erenumab. Some patients may benefit from a dose of 140 mg.

For this study and if randomized to erenumab, the investigator can treat the subject with either 70 mg or 140 mg. Dose modification/escalation will be allowed as per the approved label. Treatment and any modification should be documented. Data supporting the proposed regimen is described below.

Registration and elective clinical trials demonstrate that erenumab is safe and effective across the episodic migraine (EM) / chronic migraine (CM) spectrum, even in patients with prior preventive treatment failures (PPTFs) and medication overuse. (Goadsby et al 2017, Dodick et al 2018, Tepper et al 2017, Reuter et al 2018, Tepper et al 2017, Goadsby et al 2017, Ashina et al 2017)

Despite some numerical differences, results were largely similar across the 70 mg and 140 mg doses in the general trial population in terms of:

- Primary efficacy endpoints:

[redacted]

  - Patients across the EM–CM spectrum who received erenumab (vs placebo) achieved significantly greater reductions in monthly migraine day (MMD) frequency (Goadsby et al 2017, Dodick et al 2018, Tepper et al 2017)
  - Both the 70 mg and 140 mg doses were superior to placebo in terms of reducing MM (Goadsby et al 2017, Dodick et al 2018, Tepper et al 2017)
  - For patients with EM, a numerically greater reduction in MMD was observed with 140 mg compared with 70 mg (Goadsby et al 2017)
- Safety and tolerability profiles, as no dose-dependent adverse events were observed (Goadsby et al 2017, Tepper et al 2017, Data on File, Amgen)

However, the 140 mg dose demonstrated numerically improved results for:

- All secondary endpoints, including the number of monthly migraine days (MMDs) and the [redacted] (Goadsby et al 2017, Dodick et al 2018, Tepper et al 2017)
- Specific patient populations, e.g. patients with prior preventive treatment failures (Goadsby et al 2017, Ashina et al 2017)

[redacted]

In the erenumab clinical program, about one third of patients have reported two or more PPTFs. In this patient segment of "difficult-to-treat" patients, erenumab achieved significant improvements in MMDs, 50% responders and [redacted] and demonstrated, safety and and tolerability, supporting the use of erenumab in this population with a high unmet need. (Reuter et al 2018)

Compared with the 70 mg dose, the 140 mg dose achieved numerically greater improvements in MMDs in the PPTF subgroups assessed. Odds of achieving ≥ 50% reduction in MMDs were numerically greater for 140 mg versus 70 mg in both EM and CM studies, indicating that more "difficult-to-treat" patients can benefit from the 140 mg dose compared to the 70 mg dose. (Goadsby et al 2017, Ashina et al 2017)

Varied standard of care treatments exist and switching among therapies is common, which does not provide for long-term disease control. The duration of this study will provide data on the long-term use of erenumab as compared to SoC oral prophylactics.

4.3 Rationale for choice of control drugs (comparator)

Multiple oral prophylactic treatments are approved and vary by country. A decision to use will be based on prior treatment failure options and investigator decision. Only monotherapy will be allowed and switching treatment will be evaluated at every visit and will be based on investigator and subject discretion. As these are approved and marketed therapies, these comparators must be used in accordance with the product label/package insert with the dosing captured in the source documents and eCRF. Medications not approved for migraine prophylaxis are not allowed as SoC. If at a visit a decision is made to switch treatment, the reason and new oral prophylactic should be documented in the source and eCRF.

[redacted]

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable

4.5 Risks and benefits

Key risks and benefits are briefly summarized below. For further information, please refer to the current package insert/prescribing information and the Investigator Brochure.

As of June 2018, the safety of erenumab in migraine prophylaxis was assessed from integrated safety analyses of 2537 migraine patients exposed to at least one dose of erenumab, with a cumulative exposure of 2310.3 subject-years (SY). Overall, the safety and tolerability profile of erenumab was similar between the 140 mg and 70 mg doses and comparable to placebo. Adverse drug reactions include injection site reactions, constipation, muscle spasms, and pruritus. The majority were mild or moderate in severity and rarely led to treatment discontinuation. To date, no important risk has been identified for erenumab.

Overall, to date, there is no evidence from non-clinical and clinical data of risk of cardiovascular effects. On the theoretical basis of the mechanism of action of erenumab, CGRP receptor blockade might reduce compensatory vasodilation, particularly under ischemic conditions. Therefore, cardiovascular effects continue to be monitored.

[redacted]

Plasma levels of CGRP increase with advancement of pregnancy up to the time of delivery, followed by a sharp decline at term and postpartum in rats and humans. Endogenous CGRP may play an important role in maintaining normal fetoplacental development, fetal survival, and vascular adaptation during pregnancy. Women who are breastfeeding, pregnant, or planning to become pregnant are excluded from study participation, as well as patients who are unwilling to comply with the protocol-specified contraception requirements. All women of child-bearing potential will be screened for pregnancy at each study visit.

An external data monitoring committee was established to review the erenumab safety data for Phase 2b and Phase 3a studies, and based on these data, recommended continuation of the program. The need for a data monitoring committee (DMC) for this study was assessed, and deemed not necessary because erenumab was approved by FDA and EMA for migraine prophylaxis and the safety profile of erenumab was well characterized in 4 double-blind, placebo-controlled trials in over 2500 patients. The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and allowance of acute rescue medications.

Initial benefits for erenumab as a migraine prophylactic have been demonstrated in a Phase 2b trial (Amgen Study 20120178), in which 70 mg was established as the minimally effective dose in EM (Sun et al 2016) with a significant placebo-corrected reduction of 1.1 monthly migraine

[redacted]

days compared to baseline, as well as positive results on most secondary endpoints, including 50% responder rate.

Three additional Phase 2/3 studies, including 2 studies in EM, have been completed with erenumab, which have established 70 mg and 140 mg as being effective and safe in patients with EM or CM, with a favorable benefit/risk profile. Positive treatment effects in general were observed in a robust way across typical migraine endpoints such as change in mean monthly migraine days, > 50% (and higher) responder rates, change in migraine-specific medication use and functional improvement by established PRO scales. Results were in general highly statistically significant and clinically meaningful. Retention rates observed in clinical trials were very high (~95% with active treatment after 3 months and ~90% after 6 months with only minimal discontinuations attributed to adverse events). This feature is important, as discontinuation rates are high for current migraine prophylaxis treatments, with the main drivers of discontinuation being either lack of efficacy or tolerability issues (Blumenfeld et al 2013). As such, there is a high unmet need for a therapy that is well-tolerated, has sustained response rates and excellent compliance.

As of July 2018, two open-label extension studies (OLE) of erenumab in patients with chronic (1 year) and episodic migraine (3 years) were reported confirming sustained efficacy and a favorable safety and tolerability profile.

Overall, given the characteristics of erenumab and the large experience in clinical trials, the overall benefit-risk assessment is supportive.

5 Population

The study population will consist of adult male and female subjects with a documented history of episodic migraine (4 to 14 baseline migraine days), who have failed 1 or 2 previous migraine prophylactic treatments for lack of efficacy or tolerability.

The goal is to randomize approximately 600 subjects in approximately 100 centers worldwide. Assuming a 25% screen failure rate, approximately 800 subjects will be screened.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Adults ≥18 of age upon entry into screening.
3. Documented history of migraine (with or without aura) ≥12 months prior to screening according to the International Classification of Headache Disorders-3rd Edition (ICHD-3).
4. ≥4 and <15 days per month of migraine symptoms (based on ICHD-3 criteria) on average across 3 months prior to screening based on retrospective reporting.
5. <15 days per month of headache symptoms (i.e., migraine and non-migraine).
6. Subjects in need for switching by documented failure of 1 or 2 prophylactic treatments in the last 6 months due to either lack of efficacy or poor tolerability (see list of prophylactic categories in Exclusion Criteria 4 and definition for lack of efficacy and poor tolerability). For subjects with 1 prior treatment failure, the failure should have occurred in the last 6

[redacted]

months. For subjects with 2 prior treatment failures, the second treatment failure should have occurred in the last 6 months.

7. During baseline: Confirmed migraine frequency of 4 to 14 migraine days and <15 days of headache symptoms.
8. During baseline: ≥80% compliance with the headache diary.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Older than 50 years of age at migraine onset.
2. History of cluster headache or hemiplegic migraine headache.
3. Unable to differentiate migraine from other headaches.
4. Lack of efficacy or poor tolerability with > 2 treatments from the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:
   - Category 1: Divalproex sodium, sodium valproate
   - Category 2: Topiramate
   - Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
   - Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
   - Category 5: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
   - Category 6: Flunarizine, verapamil
   - Category 7: Lisinopril, candesartan

   Efficacy failure is defined as no meaningful reduction in headache frequency, duration, and/or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment.

   Tolerability failure is defined as documented discontinuation due to adverse events of the respective medication during the last 6 months prior to screening

   The following scenarios do not constitute lack of therapeutic response:
   - Lack of sustained response to a medication
   - Patient decision to halt treatment due to improvement
5. Used a prohibited medication from the 7 categories of prior prophylactic medications within 3 months prior to the start of and during baseline for a non-migraine indication if dose is not stable
6. Exposure to botulinum toxin in the head and/or neck region within 4 months prior to the start of the baseline period, during the baseline period.
7. Taken the following for any indication in any month during the 2 months prior to the start of the baseline period:
   - Ergotamines or triptans on ≥ 10 days per month, or

[redacted]

- Simple analgesics (non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) on ≥ 15 days per month, or
- Opioid- or butalbital-containing analgesics on ≥4 days per month.

8. Device, or procedure that potentially may interfere with the intensity or number of migraine days within 2 months prior to the start of or during baseline.
9. Active chronic pain syndromes (e.g., fibromyalgia, chronic pelvic pain).
10. History of major psychiatric disorders (such as schizophrenia or bipolar disorder) or current evidence of depression. Subjects with anxiety disorder and/or major depressive disorders are permitted in the study if they are considered by the investigator to be stable and are taking no more than 1 medication for each disorder. Subjects must have been on a stable dose within the 3 months prior to the start of the baseline period.
11. History of seizure disorder or other significant neurological conditions other than migraine. Note: a single childhood febrile seizure is not exclusionary.
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
13. Human immunodeficiency virus (HIV) infection by history.
14. History or evidence of any other unstable or clinically significant medical condition that in the opinion of the investigator would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
15. Subject has any clinically significant vital sign, laboratory, or electrocardiogram (ECG) abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation.
16. Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other re-vascularization procedures within 6 months prior to screening.
17. Score “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal Self-Injurious Behavior” (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
18. Evidence of drug or alcohol abuse or dependence based on Investigator discretion within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications or barbiturates).
19. Pregnant or nursing (lactating) women
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing with study treatment. The use of highly effective methods of contraception are required for patients treated with oral prophylactic medications that are contraindicated in women of child-bearing potential not using highly effective contraception as per their local labels (e.g. topiramate, amitriptyline, beta-blockers). As topiramate may reduce oral contraception exposure, another form of contraception (e.g. barrier method) must be used

in addition to oral contraceptive. If treated with amitriptyline, highly effective methods should be used during treatment and continued for 30 days after end of treatment

- Highly effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
  - Male partner sterilization (at least 6 m prior to screening). The vasectomized male partner should be the sole partner for that subject
  - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Basic contraception methods include:
  - All highly effective methods listed above
  - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before screening.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

21. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
22. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
23. Previous exposure to erenumab or exposure to any other prophylactic CGRP-targeted therapy prior to the study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	*Pharmaceutical Dosage Form*	*Route of Administration*	*Description*	*Sponsor (global or local)*
Core Phase				
Treatment paradigm A: Erenumab (70 mg or 140 mg monthly) (AMG334)	70 mg/1mL pre-filled syringes	Subcutaneous	Open label bulk supply. The 70 mg dose will be administered as 1mL dose from one syringe. The 140 mg dose will be administered as 2 syringes of 70 mg/mL.	Sponsor global
Treatment paradigm B: Locally Approved SoC Oral Prophylactics (daily)	Tablet/capsule	Oral use	Varies	Local
Extension Phase				
Treatment: Erenumab (70 mg or 140 mg monthly) (AMG334)	70 mg/1mL pre-filled syringes	Subcutaneous	See above for erenumab	Sponsor global

6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

At the start of the Open-Label Randomized Treatment Period (Day 1) subjects will be assigned to either erenumab (70 mg or 140 mg) or SoC oral prophylactic at the Treatment Visit in a 2:1 ratio, stratified by prior prophylactic migraine medication treatment failure (1 or 2 treatment failures due to efficacy or tolerability, with cap of 30% on 2 treatment failures) reported during the Screening/Baseline Period. In the erenumab arm, subjects may be treated with either 70 mg or 140 mg based on the investigator's assessment. This information and reason for dose selection should be documented in the source and eCRF. Erenumab and SoC oral prophylactics must be used in accordance with the locally approved product label/package insert.

Study medication will be:

- Erenumab (labelled as AMG334): pre-filled 1mL syringes (PFS) containing 70 mg/1mL of erenumab.

[redacted]

- Comparator: locally approved oral prophylactic migraine medication.

Eligible subjects that complete the Core Phase (see Section 3.0 for eligibility details) will be allowed to enter the Extension Phase and receive erenumab (70 mg or 140 mg).

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks for the Core Phase. Subjects may be discontinued from treatment earlier due to unacceptable tolerability, lack of efficacy, and/or treatment is discontinued at the discretion of the investigator or the subject, but encouraged to complete the subsequent study visits.

Eligible subjects that complete the Core Phase (see Section 3.0 for eligibility details) will be allowed to enter the Extension Phase. The duration of the Extension Phase is 52 weeks from core phase study completion at Week 52 (Week 52 through Week 104). During the Extension Phase subjects may be discontinued from treatment earlier due to unacceptable tolerability, lack of efficacy [redacted] and/or treatment may be discontinued at the discretion of the investigator or the subject. Once a patient discontinues study drug the patient will complete a final study visit as described in Table 8-2.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.2 Prohibited medication

If a subject is taking a migraine prophylactic from the 7 categories of prior prophylactic medications (Section 5.2) for a different pre-existing condition (not for migraine prophylaxis), this will be allowed as long as the subject is on a stable dose for at least 3 months prior to baseline and the pre-existing condition and corresponding treatment is documented in the source and eCRF.

Only prophylactic migraine monotherapy is allowed during the study in each arm (based on approved medications in each respective country for daily oral prophylactic medications). No other concomitant prophylactics for migraine specifically should be used, unless it is required by the HCPs to cross-titrate from one prophylactic to another.

Previously taken failed prophylactic treatment should not be re-introduced as a study drug treatment.

Use of the treatments displayed in Table 6-2 will NOT be allowed as designated due to the potential confounding of efficacy assessments.

[redacted]

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Botulinum toxin (in the head and/or neck region)	Within 4 months of the start of the baseline period and throughout the study	Discontinue study treatment. Treatment discontinuation does not imply study discontinuation.
Devices or invasive interventions (e.g., nerve blocks, occipital nerve stimulators, transcranial magnetic stimulation)	Within 2 month of the start of the baseline period and throughout the study	Discontinue study treatment. Treatment discontinuation does not imply study discontinuation.
Other Calcitonin Gene-related Peptide (CGRP) antagonists for migraine prophylaxis	Prior to the start of the baseline period and throughout the study	Discontinue study treatment. Treatment discontinuation does not imply study discontinuation.

6.2.3 Rescue medication

Subjects can continue to use “best supportive care" during the study. This can include both pharmacologic interventions (i.e., abortive treatments for acute attacks) and non-pharmacologic interventions (e.g., biofeedback, psychotherapy, acupuncture or other locally accepted and endorsed interventions for migraine).

Site staff will pre-specify the name, dose strength, and route of administration of the subject’s acute headache (rescue) medications in the subject’s eDiary. If the subject takes an acute headache medication during aura or to treat a migraine or non-migraine headache, they will select one of the pre-specified medications (or “other” medication) and enter the date of administration, the number of times the medication was taken on that date, and number of units taken.

During the Core Phase the use of rescue medication must only be recorded in the eDiary. During the Extension Phase the use of rescue medications will be entered in the concomitant medication eCRF. Relevant non-drug therapies as part of “best supportive care” use should be recorded in the eCRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) assigned by Novartis to the investigative site with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At Treatment Visit (Day 1 of Core Phase), all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion

[redacted]

criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by prior prophylactic migraine medication treatment failure (1 or 2 treatment failures due to efficacy or tolerability) reported during Screening/Baseline Period. The IRT will cap the randomization to the "2 prior treatment failure" strata to 30%.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Patients that complete the Core Phase will be allowed to enter a 52 week Extension Phase (see Section 3.0 for details).

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the CTT.

6.5 Dose escalation and dose modification

Dose escalation and dose modifications will be allowed for erenumab and the locally approved oral prophylactics to reflect approved labelling and/or current standard of care and should be documented in the subjects source documents and in the eCRF. Investigator-initiated interruptions will be considered on a case-by-case basis.

6.5.1 Dose modifications

See Section 6.5 above.

6.5.2 Follow-up for toxicities

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

[redacted]

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Core Phase

Erenumab medication is administered by the investigator or designated study staff at each visit. This information should be captured in the source document and the eCRF at each visit. All erenumab dispensed and returned must be recorded in the Drug Accountability Log. Site staff will review eDiary compliance with the patient at each visit, when applicable.

For SoC oral prophylactics, the investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable, for any reason, to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the subject. This information should be captured in the source document at each visit. SoC oral prophylactics prescribed and used must be recorded in the Drug Accountability Log for Standard of Care, to allow proper reimbursement by Novartis.

Extension Phase

After completion of the Core Phase (Week 52 Visit, Table 8-1) patients will be administered study drug at the study site (Week 52 Visit) and will then be required to have quarterly study visits at the study site. Between the quarterly visits patients will have study drug injections every 28 days either 1) administered by the site staff at brief injection visits at site or 2) self-administered at home with documented on-site training for correct injection procedure.

Note: If study drug is provided to the patient for self-administration, the patient will need to be properly trained with required documentation filed in the patient's source documents. The documentation will need to indicate that the patient was trained on the correct injection procedure, the proper drug storage and required steps for documenting the injection details including day of injection, dose location etc. The patient will then need to provide the site with the required documentation at each quarterly visit.

6.6.2 Emergency breaking of assigned treatment code

Not applicable as this is an open label study.

6.7 Preparation and dispensation

Each study site will be supplied with erenumab in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site

[redacted]

personnel will detach the outer part of the label from the packaging and affix it to the source document.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, delivery of study drug directly to a participant's home is generally permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer (e.g., self-injection or study staff administration at patients' home) the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis (see Section 7 for required training process). The dispatch of study drug from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1 month supply. In this case, regular phone calls or virtual contacts (at the time of every scheduled visit, or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Erenumab must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. During the Extension Phase erenumab may be provided to the patient at the quarterly visits if the patient opts to self-administer study medication at home. For patients opting to self-administer study medication at home documented training on the proper storage procedures is required. SoC oral prophylactics will be sourced locally and will be reimbursed by the Sponsor. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the prescribing information/package insert. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Sponsor address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable

[redacted]

6.7.2 Instruction for prescribing and taking study treatment

Refer to Section 6.1 for information on the two treatment paradigms. Erenumab will be administered as a subcutaneous (sc) injection by qualified staff during the Core Phase dosing visits. During Extension Phase subjects have the option to self-administer study drug at home for drug dispensing visits after on-site documented training). For purposes of erenumab dosing, "qm" refers to a monthly injection regimen. Erenumab administration should occur at study visits (or drug dosing visits) and any dose administrations that may occur greater than +/- 5 days from the 4-week time point (23 to 33 days after the last dose administered; due to e.g., patient unavailability or scheduling conflicts) should be discussed with Novartis prior to dosing. The anatomical sites for administration of erenumab are the upper arm, upper thigh, or abdomen; the location of the injection sites should be documented in the source document. For the comparator, the oral prophylactics will be used according to the approved indication and package insert. Prescription of previous failed drugs is not allowed.

For subjects randomized to erenumab, injections will be administered by qualified study staff at each dosing visit during the Core Phase (i.e., Treatment Week 4, Week 8, through Week 48 of the Core Phase). Subjects will be administered one of the following, depending on their randomization:

- Erenumab (70 mg or 140 mg): 70 mg/1mL syringes.
- Locally approved oral prophylactics - dose varies and expenses will be covered by the sponsor.

At the completion of the Core Phase patients that enter the Extension Phase will be administered erenumab at the site (Week 52) and will then be required to have quarterly study visits at the site at which time study drug will be administered by the site personnel. Between the quarterly visits patients will have injections of study drug every 28 days either 1) administered at site by the site staff at drug administration visits or 2) self-administered at home with documented on-site training for correct injection procedures.

The investigator must promote compliance administering the study treatment exactly as prescribed. There are no temporal restrictions for study drug administration (e.g., proximity to meals, sleep or activity). For the comparators, please refer to approved package insert for label on dosing and possible temporal restrictions.

All study treatment assigned will be recorded in the IRT. Novartis monitors will reconcile treatment assigned versus treatment administered and ensure that the information is congruent during their monitoring visits.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

[redacted]

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the prescribing information/package insert/CDS. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc).

During the COVID-19 pandemic the Investigator should discuss the home-delivery of study drug, and should provide detailed step by step instructions for the proper method for self-administration of study drug including: 1) the correct handling, 2) self-administration procedure, and 3) storage of study drug. This training may be done in person or videoconference or by telephone if patient visits to site are not possible. This training process needs to be documented in the patient's source documents with the patient's verbal/e-mail/ or chat function agreement. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.). Written informed consent must be obtained once protocol amendment 2 is approved at the site.

[redacted]

8 Visit schedule and assessments

Assessment schedule Table 8-1 and Table 8-2 lists all of the assessments and indicates with an "X" when those assessments are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Visit windows for each visit must be completed within +-5 days from Day 1 with visits occurring every 28 days as described in Table 8-1 and Table 8-2. In addition, visits need to be scheduled within the protocol specified visit windows to ensure that drug is administered within dosing windows (23 to 33 days from previous dose).

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Treatment discontinuation does not imply study discontinuation. Every effort should be attempted to ensure subjects complete the study visits event if treatment is discontinued.

If the **COVID-19 pandemic** limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again (see Section 8.3 efficacy, Section 8.4.1 Laboratory evaluations, Section 8.4.3 Pregnancy, Section 8.5.3 [redacted] and Section 8.4 Safety monitoring.

[redacted]

Table 8-1 Assessment Schedule – Core Phase

Period	Screening		Open Label Randomized Treatment													
Visit Name	Screening	Baseline	Treatment	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52 / Early Exit[10]
Days	-42 to -28	-28 to -1	Day 1	28	56	84	112	140	168	196	224	252	280	308	336	364
Weeks	-6 to -4	-4 to -1	1	4	8	12	16	20	24	28	32	36	40	44	48	52
Informed consent	X															
Medical history/current medical conditions	X															
Demography	X															
Physical Examination[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs and body measurements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X								X							X
Pregnancy Test (serum)[2]	X															X
Pregnancy test (urine)[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Central blood chemistry - Erenumab	X		X						X							X
Central blood chemistry – SoC Oral Prophylactics[3]	X		X	X[3]	X[3]	X[3]	X[3]	X[3]	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
Urine Drug Screen	X															
Columbia-Suicide Severity Rating Scale (C-SSRS)[4]	X															
Randomization			X													
Study drug administration[5]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]																
Clinical Outcome Assessment(s)[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																
Patients' Global Impression of Change						X			X			X			X	X

[redacted]

Period	Screening		Open Label Randomized Treatment													
Visit Name	**Screening**	**Baseline**	**Treatment**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52 / Early Exit[10]**
Days	**-42 to -28**	**-28 to -1**	**Day 1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Weeks	**-6 to -4**	**-4 to -1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
[redacted]																
Adverse Events[9]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Core phase[10] completion																X

X Assessment to be recorded in the clinical database or received electronically from a vendor

[1] Full exam at Screening, Week 52. Height and weight will be measured at full exam. Short physical exam at all other visits.

[2] Results of pregnancy tests (serum or urine) will be captured as source and not in eCRF.

[3] For subjects randomized to SoC oral prophylactics, central blood chemistry must be done at Screening, Treatment, Week 24, Week 52. All other visits, central blood chemistry to be done as needed for monitoring. Any additional safety measurements, if applicable, should be implemented as per label.

[4] C-SSRS will be the electronic C-SSRS designed for computer administration (web or phone)

[5] At every monthly study visit, the investigator should assess tolerability to randomized treatment (erenumab or SoC oral prophylactics) and determine if switching is appropriate. At Week 48, this will be the last dose of erenumab for subjects randomized to erenumab (monthly treatment). SoC oral prophylactics will continue to be dosed through month 12 as per label.

[6] Patients will record migraine, headache, and headache medication information daily using the provided electronic diaries.

[redacted]

[9] AE to be captured from Day 1 onward and SAE collection will be captured after informed consent is obtained.

[10] Patients that complete Core Phase visits through Week 52 may be eligible to enter the Extension Phase. All patients will receive erenumab during the Extension Phase.

[redacted]

Table 8-2 Assessment Schedule – Extension Phase

Period	Post-Trial Access Open-Label Treatment Period													
Visit Name	**Week 52**	**Week 56**	**Week 60**	**Week 64**	**Week 68**	**Week 72**	**Week 76**	**Week 80**	**Week 84**	**Week 88**	**Week 92**	**Week 96**	**Week 100**	**Week 104**
Days	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**
Weeks	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Study drug administration	X	X[1]	X[1]	X	X[1]	X[1]	X	X[1]	X[1]	X	X[1]	X[1]	X	
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/ SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con. medications / therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Pregnancy test (urine)	X			X			X			X			X	X
Extension Phase Completion														X

X Assessment to be recorded in the clinical database or received electronically from a vendor

[1] Study drug administration visit only.

[redacted]

8.1 Screening

At the Screening visit, all study subjects must be thoroughly informed about all aspects of the study, including the study treatment, visit schedule, required evaluations, eDiary compliance, and all regulatory requirements for informed consent. For details of screening assessments, refer to Table 8-1. The screening assessments must be performed within 4-6 weeks prior to first dose of study treatment to confirm subject's eligibility. Assessments cannot be performed prior to signature of the informed consent. If the subject does not fulfill all inclusion/exclusion criteria, he/she must be documented as a screening failure (Section 8.1.1). It is permissible to re-screen a subject if he/she fails the initial screening criteria. If the subject is re-screened, a new ICF must be obtained and re-screening will be documented in the subject's source documents. A new subject number will be allocated and the site will record data in a new CRF.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent but fail to enter the Open-Label Treatment Period for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page and baseline phase completion eCRF (as applicable). The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail and that the subject was not randomized.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. This will include age, sex, age, race, ethnicity, source of patient referral (if applicable), and relevant medical history/current medical condition present before signing informed consent, where possible. Diagnoses and not symptoms will be recorded.

Prior headache characteristics and previous headache medication history, including information on the suitability for migraine prophylactics and prior migraine prophylactic treatment failure history, will be collected as part of screening and baseline characteristics.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

Efficacy assessments will include:

- Migraine days
- Patient study completion

The timing and frequency of these assessments are outlined in Table 8-1. Subjects will record the efficacy information using the provided eDiary platform. To aid in compliance, it is

[redacted]

recommended that the information be completed at the same time every day and this will be pre-defined in the eDiary by the vendort. Retroactive completion will be allowed one day prior to the time of completion. Any entries >2 days old will not be allowed and will be considered missing data.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, efficacy information including PRO scales may still be collected by using the provided eDiary.

8.3.1 Migraine days

A migraine day is defined as any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria:

1. ≥2 of the following pain features:
    - Unilateral
    - Throbbing
    - Moderate to severe
    - Exacerbated with exercise/physical activity
2. ≥1 of the following associated symptoms:
    - Nausea and/or vomiting
    - Photophobia and phonophobia

If the subject took a migraine-specific medication (ie, triptan or ergotamine) during aura, or to treat a headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

To further characterize a migraine day, the following information will be collected:

- Date and time of start of headache (ie, migraine or non-migraine headache)
- Date and time of end of headache
- Worst pain severity per headache
- Pain features (eg, one-sided, throbbing, worsens with exercise/physical activity)
- Symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia, vertigo)
- Use of acute headache medications (medication name (from pre-entered list), date and time of dosing, number of times taken of each date, number of units taken).
- For women of child-bearing potential, start and end dates of monthly menses

8.3.2 Appropriateness of efficacy assessments

The definition of migraine day (Section 8.3.1) is consistent with the diagnostic criteria of migraine and probable migraine according to the International Classification of Headache (ICHD-3). The monthly migraine days will be calculated using migraine day data collected from the eDiary. Migraine days are commonly used as a primary endpoint in pivotal trials as acknowledged in the IHS guidelines for controlled trials of drugs in migraine (Tfelt-Hansen et al 2012) and is consistent with the erenumab clinical development.

[redacted]

As the mean change in monthly migraine day (MMD) however describes a population-based measure and given the natural variability in migraine trials often is associated with small effect sizes, clinically an important complementary information is the proportion of subjects that achieve a certain clinical benefit, which is usually described with achieving at least a 50% reduction of migraine days compared to the individual baseline ("50% responder rate"). In pivotal trials, 50% (or higher) responder rates are usually included as secondary or key secondary outcomes. Given that this trial is not considered a pivotal trial but rather should provide clinical guidance, the 50% reduction was considered more relevant and therefore chosen as part of the primary endpoint. The percentage of patients completing the study (retention rates) was selected as part of the composite endpoint based on the long-term data from earlier clinical studies (20120255 and 20120296) confirming retention remains high for erenumab treated patients at one year (75-80%) and that efficacy is continued over time, which would be clinically relevant when compared to available prophylactic treatment.

[redacted]

8.4 Safety

Safety assessments are specified below with the assessment schedule (Table 8-1 and Table 8-2) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section Section 10.1).

During the **COVID-19 pandemic** that limits or prevents on-site study visits, regular phone or virtual calls will occur (at the time of every schedule visit or more frequently if needed) for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

Table 8-3 Safety Assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical exam will be at Screening, and Week 52 A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from Baseline except where a complete physical examination is required (see above).

[redacted]

	Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Vital signs	Vital signs include BP and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Appendix 1.
Height & weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured during full physical exams.
Columbia Suicide Severity Rating Scale	See Section 10.2.2

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Section 16.1.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible, the collection of samples may be modified by Novartis and will be communicated to the Investigator (e.g., local lab collection of samples).
Urine Drug Screen

Patients will be tested for substances of abuse at initial screening to confirm patient eligibility. During the study, urine drug tests can be performed at the investigator's discretion based on clinical suspicion. Urine samples will be analyzed by the central laboratory. If a patient has a positive urine drug screen during the study (except for certain prescribed information), the investigator should consider discontinuation from the investigational product.

8.4.2 Electrocardiogram (ECG)

ECGs will be recorded as outlined in the central ECG reading manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) as reported by the central reader should be used for clinical decisions.

Single 12 lead ECGs will be collected. The original ECGs printed on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

[redacted]

Each ECG tracing must be labeled with study number, patient initials, subject number, date and time, and filed in the study source documents. For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety finding and forwarded to the central ECG laboratory for assessment. Clinically significant ECG findings pre-dose must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/current medical conditions/AE eCRFs as appropriate.

8.4.3 Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Serum pregnancy tests will be performed at the Screening and Week 52 visits with urine pregnancy tests performed as described in Table 8-1 and Table 8-2.

During COVID-19 pandemic, if a patient cannot visit the site to have pregnancy tests conducted the patient may complete a urine pregnancy test at home and report the result to the site. It is important that patients are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the patient so that the Site is informed of the pregnancy test results.

8.4.4 Appropriateness of safety measurements

The safety assessments were selected based on the safety profile of erenumab as reported in the development Investigator Brochure, package insert/prescribing information, and are standard for this patient population and drug class.

For SoC oral prophylactics, additional safety measurements, if applicable, should be implemented as per label.

8.5 Additional assessments

The following additional assessments will be done. The timing and frequency of these assessments are outlined in Table 8-1:

- Clinical Outcome Assessments/Patient Reported Outcomes
- [redacted]

8.5.1 Clinical Outcome Assessments (COAs)

Clinical Outcomes Assessments (COAs) will be collected by subjects using an electronic diary (eDiary)/site tablet at various frequencies. The eDiary will collect the following daily, at home:

- Date and time of start of headache (i.e., migraine or non-migraine headache)
- Date and time of end of headache
- Worst pain severity per headache
- Pain features (e.g., one-sided, throbbing, worsens with exercise/physical activity)

[redacted]

- Symptoms (e.g., aura, nausea, vomiting, photophobia, phonophobia)
- Use of acute headache medications (medication name from pre-entered list, date of dosing, dosing and frequency)

The eDiary will categorize headache events as migraine days or headache days based on the definitions below:

- Headache Day - any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as the following:
  - a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
  - a qualified non-migraine headache, which is a headache that lasts ≥30 minutes and is not qualified as a migraine headache, or
  - a headache of any duration for which acute headache treatment is administered.
- Migraine Day - See Section 8.3.1 for details.

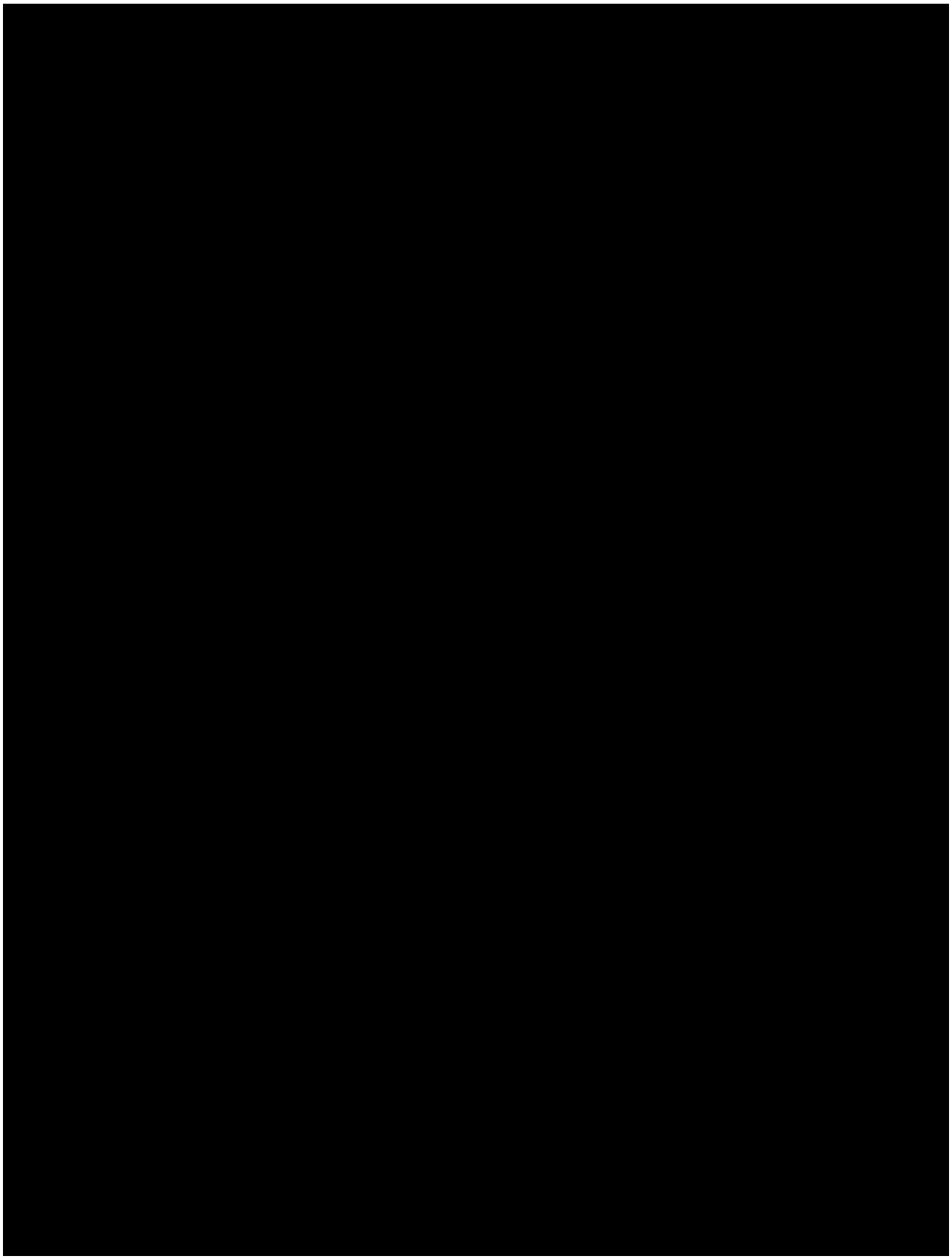
The eDiary will also collect the following patient-reported outcomes (PROs) and questionnaires:

- Patients' Global Impression of Change (PGIC)

[redacted]

The site study staff will train the patient on proper use of the eDiary (e.g., turning on/off, navigation, data transmission, helpdesk, etc.) and completing the questions. The patient will be instructed to interact with the eDiary daily during the Baseline Period and Open-Label Treatment Period and to bring the eDiary to every study visit. At Day 1/Treatment, the investigator will use the patient's eDiary to review all data entered during the Baseline Period and confirm the relevant inclusion/exclusion criteria. The eDiary manual should be used to locate additional details.

[redacted]



[redacted]

8.5.1.7 Patients' Global Impression of Change

The Patients' Global Impression of Change (PGIC) is a global assessment by the subject of the change in clinical status since the start of treatment. The PGIC is assessed periodically through the treatment period and at the end of the treatment period. The PGIC ratings are as follows:

1 = No change (or condition is worse)

2 = Almost the same, hardly any change at all

3 = A little better, but no noticeable change

4 = Somewhat better, but the change has not made any real difference

5 = Moderately better, and a slight noticeable change

6 = Better, and a definite improvement that has made a real and worthwhile difference

7 = A great deal better, and a considerable difference that has made all the difference

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section

- Any situation in which study participation might result in a safety risk to the subject

In addition during the Extension Phase, study treatment should be discontinued under the following circumstances

- Patient is no longer clinically benefitting from treatment in the opinion of the investigator [redacted]

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at site visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

NOTE: Subjects that wish to enter the Extension Phase and receive PTA access to erenumab need to remain in the trial and complete all study visits through Week 52 as described in Table 8-1. The investigator would then assess eligibility of the patients as described in Section 3.0.

9.1.2 Discontinuation of study

For patients that will discontinue from the study they need to complete the Early Exit Visit / Week 52 visit at the time of study discontinuation.

9.1.2.1 Replacement policy

Subjects will not be replaced on study.

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and

[redacted]

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed and until the end of the study.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for contacting the patient, when the patient should stop taking drug, when the patient should come for a final visit) and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

[redacted]

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. A subject will be considered to have completed the Core Phase when the subject has completed the Week 52 Visit. A subject will be considered to have completed the Extension Phase when the subject completes the Week 104 Visit.

After study completion, post-trial access to erenumab will be offered to the study participants as needed.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Adverse event collection will begin at Treatment/Day 1 (treatment emergent adverse events). Any event prior to Treatment/Day 1 should be captured in Medical History.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events. Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments. Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade.
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected’. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject

[redacted]

3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome
    a. not recovered/not resolved;
    b. recovered/resolved;
    c. recovered/resolved with sequelae;
    d. fatal; or unknown.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the prescribing information/package insert/CDS.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

[redacted]

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening - Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit must be reported to Novartis safety

[redacted]

within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis*/sponsor* may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition). Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

[redacted]

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring

Please refer to Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-3. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unplanned local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough investigation of the liver event -
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more

[redacted]

detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate.

10.2.2 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS will be administered at Screening.

A validated version of the C-SSRS will be used to capture self-reported C-SSRS data via an interactive voice response telephone system (eC-SSRS). The eC-SSRS uses a detailed branched logic algorithm to perform the C-SSRS subject interview, evaluating each subject's suicidality ideation and behavior in a consistent manner. At the conclusion of each assessment, the investigator will receive a detailed eC-SSRS Findings Report via e-mail or fax. If the system assesses the subject as having positive suicidal signs, the investigator will be immediately notified by either fax, email and/or via telephone.

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the suicidal ideation section of the C-SSRS or "yes" on any item of the suicidal behavior section, the subject must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the subject is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a subject answers "yes" to one of the questions in the suicidal behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the suicidal behavior section) should be reported as AEs and assigned the appropriate severity grade.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site. All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis. ECG readings will be processed centrally and the results will be sent electronically to Novartis. Diary data will be entered into an electronic diary by the subject. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or site medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

[redacted]

assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The core phase and extension phase data will be analyzed separately.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received. Open label extension phase analysis set will include subjects who consented to enter Extension Phase and who have taken at least one dose of erenumab in Extension Phase.

12.2 Subject demographics and other baseline characteristics

Demographic variables and other baseline characteristics including previous migraine treatments will be summarized for FAS. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each treatment group and for all participants (total). The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants (total). In addition, all relevant medical history will be summarized following the same strategy.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

A data listing and a summary of the investigational drug (erenumab or active comparator) administered will be provided. Unless otherwise specified, patients assigned to 70 mg or 140

[redacted]

mg erenumab dose will be analyzed together under one treatment arm erenumab. The analysis by dose will be detailed in SAP as needed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

A data listing and summary of rescue medications will be provided by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to evaluate the effect of erenumab vs SoC oral prophylactic medications on the net benefit, a measure of sustained long-term benefit in these two treatment paradigms of migraine prophylactic agents.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is the proportion of subjects achieving net benefit, defined as completion of one year on the initial treatment AND achieving at least a 50% reduction from baseline in monthly migraine days in the last month (month 12).

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analyses will compare the proportion of subjects in FAS who achieve a net benefit (defined in previous section) between erenumab vs SoC oral prophylactic medications.

To be tested is the null hypothesis that net benefit odds ratio = 1, versus the alternative hypothesis: net benefit odds ratio $\neq 1$.

A Cochran-Mantel-Haenszel (CMH) test stratified by number of previous treatment failures (1 vs. 2) will be used under a 2-sided significance level of 0.05 to evaluate the association between the net benefit rate and the treatment. The p-value of the test, and the estimated odds ratio between erenumab and active comparator, as well as its 95% confidence interval, will also be reported.

The details on primary and supplementary estimand will be provided in estimand charter or statistical analysis plan (SAP).

12.4.3 Handling of missing values/censoring/discontinuations

Subjects with missing monthly migraine day data at month 12 of treatment, and subjects that discontinue initial treatment prior to month 12 will be imputed as non-responders (not achieving a net benefit).

12.4.4 Sensitivity and Supportive analyses

The sensitivity and supportive analysis will be detailed in SAP.

[redacted]

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

- **Proportion of subjects completing the treatment period at month 12 on the initially assigned treatment**

This variable will analyzed same as that of the primary endpoint.

- **Global satisfaction as measured by PGI at month 12 for subjects completing treatment period on initially assigned treatment**

Patient will be considered as responder if PGI-I score is 5, 6, or 7. Proportion of responders based on PGI-I score at month 12 will be analyzed same as that of the primary endpoint.

- **Cumulative average change from baseline on the monthly migraine days during the treatment period** for subjects on the initially assigned treatment **(month 1-12)**

The average of monthly migraine days will be obtained cumulatively at each month across 12 months (e.g. at month 2 the average will be based on data from month 1 and 2; at month 3 the average will be based on month 1 to 3 and so on). The cumulative average change from baseline on the monthly migraine days will be derived using difference between cumulative average at each month and baseline monthly migraine days. The change from baseline will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

The on-treatment period lasts from the date of first administration of study treatment to 112 days after the date of the last actual administration of any study treatment.

[redacted]

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment-emergent adverse events (events started after the first dose of study medication) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

[redacted]

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment.

12-lead ECG

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.5.3 Pharmacokinetics

Not applicable.

12.5.4 DNA

Not applicable.

12.5.5 Biomarkers

Not applicable.

12.5.6 PK/PD relationships

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

Not Applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary variable, rate of net benefit. The details of hypothesis testing are described in Section 12.4.2.

A 2-sided test with significance level 0.05, and a 2:1 randomization ratio are considered. A sample size of 591 (394 erenumab arm; 197 control arm) is required to achieve 90% power to reject the odds ratio of 1 set by the null hypothesis when the odds ratio is actually 2, and success rate in control arm is 0.18.

An odds ratio of 2 and control rate of 0.18 is based on more conservative assumptions for rate of net benefit than observed previously (for erenumab in studies NCT02456740, NCT01952574, and oral prophylactics in Hepp et al 2017, Shei et al 2015), resulting in a rate difference of 12%. Sample size calculations were done using PASS 11 and Cochran-Mantel-Haenszel test.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

In the US, Amgen will be the sponsor and all responsibilities for the conduct of this clinical study will be transferred to Novartis. In all other countries, Novartis will be the sponsor and maintain all responsibilities for the conduct of the clinical study.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement

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to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (***defined as last patient last visit***) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

An initial study report will be prepared and finalized for all data from the Core Phase. A second and study report will be prepared for the Extension Phase after all patients have completed their respective last visit (LPLV) of the Extension Phase.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request

(2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet p. 1211-1259.

Ashina M, Dodick D, Goadsby PJ, et al (2017) Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. Neurology p. 1237-1243.

Ashina M, Tepper S, Brandes JL, et al (2017) Efficacy of erenumab in chronic migraine patients with prior prophylactic treatment failure: Subgroup analysis of the Phase 2, randomised, double-blind, placebo-controlled study. Cephalalgia. 2017;37:326-328. Poster PO-01-180 presented at IHS 2017.

[redacted]

Blumenfeld AM, Bloudek LM, Becker WJ, et al (2013) Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache p. 644-55.

Brandes JL, Diener H, Dolezil D, et al (2017) Chronic Migraine Treatment with Erenumab: Responder Rates. Headache. 2017; 57(S3): 113-226. Poster PS33 presented at AHS 2017.

[redacted]

Data on File, Amgen; Integrated Summary of Safety 5.3.5.3 AMG334

Dodick DW, Ashina M, Brandes JL, et al (2018) ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia p. 1026-1037.

Durham PL (2006) Calcitonin gene-related peptide (CGRP) and migraine. Headache p. S3-8.

Goadsby PJ, Paemeleire K, Broessner G, et al (2017) Efficacy of erenumab in subjects with episodic migraine with prior preventive treatment failure(s). Cephalalgia. 2017;37(1S):1-24. Oral abstract OC-MC-002 presented at IHS 2017.

Goadsby PJ, Reuter U, Hallström Y, et al (2017) A Controlled Trial of Erenumab for Episodic Migraine. N. Engl. J. Med. p. 2123-2132.

Gooriah R, Nimeri R, Ahmed F (2015) Evidence-Based Treatments for Adults with Migraine. Pain Res Treat p. 629382.

Hepp Z, Dodick DW, Varon SF, et al (2017) Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis. Cephalalgia p. 470-485.

[redacted]

Hepp Z, Rosen NL, Gillard PG, et al (2016) Comparative effectiveness of onabotulinumtoxinA versus oral migraine prophylactic medications on headache-related resource utilization in the management of chronic migraine: Retrospective analysis of a US-based insurance claims database. Cephalalgia p. 862-74.

Reuter U, Goadsby P, Lanteri-Minet M (2018) Efficacy and Safety of erenumab in episodic migraine patients with 2-4 prior preventive treatment failures: Results from the Phase 3b LIBERTY Study. Poster 009 presented at AAN 2018..

Reuter U, Goadsby P, Lanteri-Minet M, et al (2018) Efficacy and safety of erenumab in episodic migraine patients with 2–4 prior preventive treatment failures: Results from the Phase 3b LIBERTY study. Presented at AAN 2018.

Shei A, Woolley JM, Desai PR, et al (2015) Description of prophylactic drug utilization patterns in migraine patients. Value in Health p. A285.

Sun H, Dodick DW, Silberstein S, et al (2016) Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol p. 382-90.

Tepper S, Ashina M, Reuter U, et al (2017) Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol p. 425-434.

Tepper SJ, Diener H, Ashina M, et al (2017) Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse. Headache. 2017;57(S3):113-226. Poster PS32 presented at AHS 2017.

Tfelt-Hansen P, Pascual J, Ramadan N, et al (2012) Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia p. 6-38.

Wang X, Yue TL, Barone FC, et al (1995) Discovery of adrenomedullin in rat ischemic cortex and evidence for its role in exacerbating focal brain ischemic damage. Proc. Natl. Acad. Sci. U.S.A. p. 11480-4.

[redacted]

Zimmermann U, Fischer JA, Frei K, et al (1996) Identification of adrenomedullin receptors in cultured rat astrocytes and in neuroblastboma x glioma hybrid cells (NG108-15). Brain Res. p. 238-45.

[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Table 16-1 Clinically Notable Laboratory Values

Laboratory Variable	Gender (M/F/Both)	Standard Units	SI Units
LIVER FUNCTION AND RELATED VARIABLES			
SGOT (AST)	F	>93 U/L	>93 U/L
SGOT (AST)	M	>111 U/L	>111 U/L
SGPT (ALT)	F	>90 U/L	>90 U/L
SGPT (ALT)	M	>123 U/L	>123 U/L
Total bilirubin	Both	>3.6 mg/dL	>63 mmol/L
Alkaline Phosphatase	F	>832 U/L	>832 U/L
Alkaline Phosphatase	M	>1032 U/L	>1032 U/L

[redacted]

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-2 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	
	• 3 x ULN < ALT / AST £ 5 x ULN · 1.5 x ULN < TBL £ 2 x ULN
LIVER EVENTS	
	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	• Any clinical event of jaundice (or equivalent term)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Note: INR (International Normalized Ratio) measurements are not collected as part of routine lab assessments. If a patient has a liver event please consider to collect an INR to aid in assessing severity.

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Table 16-3 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		

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Criteria	Actions required	Follow-up monitoring
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

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